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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/680,996

10/07/2003

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09/25/2008

EXAMINER

CLAYTOR, DEIRDRE RENEE

ART UNIT

PAPER NUMBER

1617

MAIL DATE

DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/680,996	Applicant(s) TATTON ET AL.	
	Examiner Renee Claytor	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 July 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9 and 11-13 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9 and 11-13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) ☐ Notice of References Cited (PTO-892) | 4) ☐ Interview Summary (PTO-413) |
| 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) ☒ Information Disclosure Statement(s) (PTO/SB/08) | 5) ☐ Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>7/24/2008</u> . | 6) ☐ Other: _____ |

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/24/2008 has been entered.

Response to Arguments

Applicants argue that the 35 USC 112 rejection is improper because the specification teaches that to prevent neuron death or degeneration, one administers brimonidine. Applicants assert that because the method of the invention shows less neuron loss, that this is sufficient to achieve the claimed limitation of "prevent". Applicants argue that if one prevents some neuron loss, then one can successfully treat these conditions. Applicants discuss labeling of the FDA of drugs that include the word "prevention" in its labeling.

In response to the above arguments, the Examiner would like to first point out that the definition of "prevent" is "to keep from occurring; avert; hinder" (taken from dictionary.com). Therefore, the claim recitation of preventing death or degeneration of neural cells (claims 6 and 7) would require that death or degeneration of neural cells would never occur. Of which there is no support for this in the specification, there is

Art Unit: 1617

only support for decreasing the amount of neuronal death that occurs. Therefore, there would be undue experimentation to practice this limitation of the invention because one would have to determine that a person will have neuronal death (associated with Parkinson's disease in this case) and that administering brimonidine would hinder this neuronal death from ever occurring. Therefore, showing that there is some neuron loss is not a sufficient showing that prevention of neuronal loss occurs. Further, decreasing neuronal death does not prevent Parkinson's disease, it only decreases the severity of the disease. Preventing neuronal death would cause the disease to never occur, and as pointed out by Kedar in the previous rejection, there are no prevention strategies for Parkinson's disease. Further, the argument concerning FDA labeling is not persuasive because requirements for FDA labeling differ from patent requirements.

The Applicant's arguments over the 35 USC 103 rejection have been fully considered. In particular, Applicants argue that the Arnsten references does not stand proposition that clonidine can be used to treat neurodegenerative conditions because the studies were conducted in normal aged animals and not animals with a neurodegenerative condition. It is further argued that Arnsten provides no evidence that clonidine is effective in protecting neurons of the substantia nigra, VTA or locus ceruleus. Applicants argue that Chan-Palay only teaches that there is degeneration of the locus ceruleus in certain patients with senile dementia of the Alzheimer's type and in Parkinson's disease and that Olejnik only teaches that brimonidine has a neuroprotective activity through an unknown mechanism.

Art Unit: 1617

In response to the above arguments, it is noted that Arnsten does teach normal aged animals conducting experiments such as the delayed-response task. Experiments in aged animals is common in testing performance for learning and memory associated with Alzheimer's disease. The authors conclude adrenergic agonists may be helpful for patients with Alzheimer's disease because the results from the studies show that clonidine is useful in treating age-related cognitive disorders (of which Alzheimer's is considered an age-related cognitive disorder). Further, Arnsten teaches that clonidine acts at sites throughout the nervous system and that some of the drug effects in the study may be localized in the brain region that is the prefrontal cortex surrounding the principal sulcus. Arnsten explains a study on page 1276 in which the dorsolateral prefrontal cortex surrounding the principal sulcus was ablated and treatment with clonidine did not improve performance in the delayed-response task. Arnsten further teaches that the prefrontal cortex is reported to contain the highest concentration of postsynaptic α_2 receptors in the rodent brain. Applicants describe in their specification that VTA contains neurons which project to sites such as the prefrontal cortex (page 8) which is the portion of the brain associated with higher cognitive functions. Therefore Arnsten does teach protection of neurons because claim 6 reads on protecting neurons projection to or from a region of the brain selected from the group consisting of the substantia nigra, the locus ceruleus and the VTA. In addition, Chan-Palay was simply used to teach that the locus ceruleus has been shown to be affected in disorders such as Parkinson's disease and Olejnik reference was used to teach that brimonidine is an

Art Unit: 1617

α 2 agonist. Accordingly, the modified rejection is given below for Applicants convenience.

Applicant's arguments regarding the Obviousness Double Patenting rejection are found persuasive and the rejection is withdrawn. However, see the new grounds of rejection given below.

Claim Objections

Claim 3 is objected to because of the following informalities: "locus sereleous" should be spelled "locus ceruleus". Appropriate correction is required.

Claim Rejections – 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 6-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement for the prevention death or degeneration of neural cells projecting to or from a region of the brain selected from the group consisting of the substantia nigra, the locus ceruleus and the ventral tegmental area (VTA). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. “The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims”, *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

(1) The nature of the invention and breadth of the claims: The nature of the invention and breadth of the claims is drawn to a method for preventing death or degeneration of neural cells in the brain comprising administration of brimonidine.

(2) The amount of direction or guidance presented and the presence or absence of working examples: In the instant case, no working examples are presented in the specification as filed showing how to prevent death or degeneration of neural cells comprising the administration of brimonidine. The specification on pages 45-47 details studies performed in animal models showing that when brains were removed from the animals it was shown that MPTP-treated animals have fewer neurons than untreated animals and brimonidine treated animals have significantly less neuron loss. In particular, it is taught that Control animals had an average neuron count of 60. Animals treated with MPTP had an average neuron count of 25 and animals treated with brimonidine had an average neuron count of 32. Therefore, brimonidine showed some improvement in the behavioral models and showed less neuron loss in MPTP

Art Unit: 1617

treated animals, but did not show total prevention of either Parkinson's disease or Alzheimer's disease. Further, the specification does not teach a total prevention of neuron loss because there is still a measurable amount of neurons that have been depleted (in the instant case 38 neurons). A showing of prevention of any disease would require an unreasonable anticipation that a patient is going to have a particular disorder, i.e. Parkinson's or Alzheimer's disease.

(3) The state of the prior art: The state of the art regarding treating various neurodegenerative disorders is relatively high (Hilbush, B.S. et al., NeuroRx: The Journal of the American Society for Experimental NeuroTherapeutics, 2, 627-37, 2005). However, the state of the art regarding prevention of the death or degeneration of neurons of the present invention is highly underdeveloped (see Kedar NP, J of Postgrad Med (2003); 49: 236-245). Kedar discusses that no preventative or long-term effective treatment strategies are available for such neurodegenerative conditions such as Parkinson's disease or Alzheimer's disease (see pg. 236, first paragraph). Kedar discusses that protecting neurons from further damage in the early phase of the disease may help to reduce the rate of progression of symptoms of Parkinson's and Alzheimer's disease (pg. 236, first paragraph). Kedar further states that prevention strategies can be developed if the risk and protective for Parkinson's and Alzheimer's disease are known, but currently the only risk factors known are familial and possible diet (see pg. 241, last paragraph).

(4) The quantitation of experimentation necessary: Claims 3 and 6-9 read on a method for preventing death or degeneration of neural cells with the α_2 -receptor

Art Unit: 1617

agonist brimonidine. As discussed above, the specification provides examples for treating neuron loss in Parkinson's disease and Alzheimer's disease, but the specification fails to provide sufficient support for prevention of death or degeneration of neural cells. Applicant fails to provide information sufficient to practice the claimed invention, absent undue experimentation. Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Arnsten et al. (Science, Vol. 230; pgs. 1273-1276) in view of Olejnik et al. (U.S. Patent 6,627,210) and Chan-Palay et al. (The Journal of Comparative Neurology, 287: 373-392).

Arnsten et al. teach that there is a loss of catecholamines (norepinephrine) in Alzheimer's disease and that pharmacological treatments may ameliorate the cognitive

Art Unit: 1617

deficits (pg. 1274, Col. 1 and 2). Arnsten et al. teach that the α_2 -receptor agonist clonidine and adrenergic agonists in general will be helpful for patients with Alzheimer's disease (pg. 1276, Col. 2). It is taught that cell deterioration occurs in the locus ceruleus and in particular the portion innervated by the prefrontal cortex (meeting the limitation of claims 3 and 6; pg. 1276, Col. 2). Arnsten also teaches that effects of clonidine may act through the prefrontal cortex surrounding the principal sulcus (page 1275), of which projections from the prefrontal cortex lead to the VTA as Applicants teach in page 8 of their specification. Accordingly, it is deemed obvious that the effects of the drug are treating the neural cells of the brain projecting to or from a region of the brain selected from the locus ceruleus and the VTA (in claim 6).

Arnsten et al. do not teach the administration of brimonidine or the treatment of Parkinson's disease.

Olejnik et al. teach compositions comprised of α_2 -receptor agonists as the active ingredient, with the preferred α_2 -receptor agonist being briminodine (Col. 5, lines 45-48 and claim 1). Other suitable α_2 -receptor agonists include clonidine (Col. 5, line 26).

Chan-Palay et al. teach that the locus ceruleus is an important source of norepinephrine and is shown to be affected in several neurologic disorders, including Parkinson's disease and Alzheimer's disease (pg. 373, first paragraph).

Accordingly, it would be obvious to one having ordinary skill in the art at the time of the invention, to combine the teachings of Arnsten et al, which teaches the treatment potential of an α_2 -receptor agonist in Alzheimer's disease and further teaches that the α_2 -receptor agonist is having effects on neurons in brain regions projection to or from

Art Unit: 1617

the locus ceruleus or VTA with the teachings of Olejnik et al. which teach brimonidine as an α_2 -receptor agonist. One would be motivated to combine the references with a reasonable expectation of success because of the teaching that an α_2 -receptor agonist can treat Alzheimer's disease and clonidine and brimonidine are both α_2 -receptor agonists. Further, it would be obvious to that α_2 -receptor agonists would beneficially treat Parkinson's disease because of the teachings of Chan-Palay which teaches that the locus ceruleus is involved with disorders such as Parkinson's disease. One would be motivated to treat Parkinson's disease with brimonidine because Chan-Palay teaches that norepinephrine in the locus ceruleus is implicated in Parkinson's and Alzheimer's disease, and Arnsten et al. teach that cell deterioration occurs in the locus ceruleus in Alzheimer's disease and that α_2 -receptor agonists in general are a beneficial for treatment; therefore, there is a reasonable expectation of success because both diseases have similar pathologies.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

Art Unit: 1617

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 4-5, 11-13 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4-6 and 8-9 of copending Application No. 10/881,761. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application are drawn to treating Parkinson's or Alzheimer's disease with brimonidine and the claims of application 10/881,761 are drawn to a method of treating a neurodegenerative condition comprising the administration of an α_2 -receptor agonist that includes brimonidine, along with an α_2 -receptor antagonist. The applications are obvious over the other because both applications are drawn to administering an α_2 -receptor agonist for the treatment of neurodegenerative conditions such as Alzheimer's disease.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Renee Claytor whose telephone number is (571)272-8394. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Renee Claytor

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1617